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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,751	10/30/1998	OYSTEIN FODSTAD	4885.55USWO	8143

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	23

DATE MAILED: 03/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/125,751	Fodstad et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 10, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 6-8, 13-16, 18-23, 25, and 26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 6-8, 13-16, 18-23, 25, and 26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Amendment filed January 8, 2002 (Paper No. 22) in response to the Office Action of August 8, 2001 (Paper No. 20) is acknowledged and has been entered. It is noted that the claims as originally filed recited claims 1-11 and 13. Because the claims were not numbered consecutively, under 37 CRF 1.126 they have been renumbered 1-12, respectively. In the Paper No. 11, claim 14 was added. Because this claim was not numbered consecutively it has been renumbered, under 37 CRF 1.126 as claim 13. In Paper No. 19, claims 15-25 were added. Because these claims were not numbered consecutively they have been renumbered, under 37 CRF 1.126 as claims 14-24. In Paper No. 22, claims 12 (drawn to a kit), 17 (drawn to cell population comprising peripheral blood cells or bone marrow cells), 21 (drawn to a cancer patient , and 24 (drawn to low toxicity of CD34+ cells) have been canceled, claims 1, 3, 6-8, 13-16, 18, 20-21 have been amended and newly added claims 26 and 27 which have been renumbered under 35 CFR 1.126 as claims 25 and 26 have been added. Claims 1, 3, 6-8, 13-16, 18-21, 22-23 and 25-26 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections

3. The amendment filed January 8, 2002 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

1. Harvesting nucleated cells from peripheral blood or CD-34+ cells;

2. Or other immature/early progenitor cells from blood containing multipotent stem cells;

3. Wherein the immunotoxin is directed to epitopes on a combination of these.

Applicant is required to cancel the new matter in the response to this Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. Claims 1, 6-8, 13-14, 20-23 and 25-26 are rejected under 35 USC 112, first paragraph, for the reasons set forth in Paper No. 20, Section 6, pages 3-4, and further for the reasons below because the specification, while being enabling for a method of killing breast cancer cells or other carcinoma cells *in vivo* and *ex vivo* wherein the method comprises incubation with MOC31-PE and BM7-PE, does not reasonably provide enablement for a method of killing breast cancer cells or other carcinoma cells *in vivo* and *ex vivo* wherein the method comprises incubation with immunotoxins directed against an EGP2 antigen and a MUC1 antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of killing breast cancer cells or other carcinoma cells comprising incubation with immunotoxins directed against an EGP2 antigen and a MUC1 antigen. This includes any antibody to any epitope on either EGP2 antigen and MUC1 antigen. The specification teaches that the present

invention relates to purging harvested stem cell populations in cases of solid tumors wherein the method comprises exposing said cell populations to two or more antibodies conjugated to bacterial toxins wherein the antibodies are directed to target cell-associated antigens (p. 4, lines 7-11) and that due to the high specific activity of the disclosed immunotoxins *in vitro*, it seems possible to administer the mixture for *in vivo* treatment of patients suffering from different types of carcinomas (p. 12, lines 31-33). The specification discloses two immunotoxins, MOC31-PE and BM7-PE (page 13, lines 5-7 and page 15, lines 1-8) and exemplifies individual use of the immunotoxins for killing breast cancer cells (see Examples). The specification discloses two other immunotoxins which were not chosen for either *in vivo* or *in vitro* characterization. NrLu10-PE binds to the same antigen as MOC31-PE but is less active. The specification does not teach whether or not NrLu10-PE is selective for the antigen as expressed on tumor cells compared to normal cells or discuss its toxicity to normal cells. BM2-PE binds to the same antigen as BM7-PE concomitant with a very low toxicity for normal cells (para bridging pages 5-6). One cannot extrapolate the teaching of the specification to the scope of the claims because both EGP2 and MUC1 are ubiquitously expressed in normal cells and it would be expected that any immunotoxins, other than those specific for the antigens expressed on tumor cells would be sequestered by the ubiquitously expressed antigens on normal cells. Thus, it could not be predicted that a sufficient concentration of immunotoxins would become bound to tumor cells so that the invention would function as claimed. Further the effects of *in vivo* immunotoxin administration, wherein the immunotoxin is targeted to a ubiquitously

expressed antigen, cannot be predicted. This is evidenced by Apostolopoulos et al (Cancer Lett. (Shannon, Irel.), 1995,90:21-26) who specifically teach that MUC1 is highly expressed in breast cancer, has a ubiquitous distribution and due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1antibodies which give a differential reaction on cancer compared with normal tissue (see abstract). This is further evidenced by McClaughlin et al, (Cancer Research 2001, 61:4105-4111) who specifically teach that EGP-2 is commonly targeted for immunotherapy of carcinomas because it is strongly expressed by most carcinomas. EGP2. However, EGP-2 is also expressed in most normal epithelia. MOC31 antibody specifically localizes to EGP-2 positive tumors and does not localize in normal tissues (see abstract). The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicant's arguments drawn to the rejection of claims 1 and 6-8 in Paper No. 20, Section 6, pages 3-4 are relevant to the instant rejection.

Applicant argues that (a) the amendment of the claims to "cancer cells expressing the same target antigens" overcomes the rejection. Since the invention has been exemplified both *in vivo* and *in vitro* with MOC31 and BM7, one skilled in the art would expect that other cells expressing the same antigens would be

similarly affected. The argument has been considered but has not been found persuasive because although one would expect that other types of carcinomas expressing the same epitopes would be killed, it cannot be predicted that other antibodies to the claimed antigens would have the same effect, especially since it appears that both MOC31 and BM7 (the only disclosed antibodies which thus have "high specific activity" for the tumor antigens) are selective for antigen expressed on tumor cells. In particular, it is notoriously well known in the art that both MUC1 and EGP2 are ubiquitously expressed in normal tissue and that only certain epitopes of those antigens are tumor specific, therefore not all antibodies to the two epitopes would be expected to function as broadly claimed since the specification teaches only two high specific activity antibodies, both of which appear to be tumor cell specific antibodies. Further, Applicant has not addressed the issue raised drawn to the restriction against using MOC-31 for any purpose other than research since the claims are drawn to treatment and not to research.

5. Claims 3, 15, 16, 18, 19 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 20, Section 7, pages 4-5, Paper No. 16, Section 5, page 4 and Paper No. 13, Section 7, pages 6-9, drawn to the rejection of claim 3.

Applicant's arguments drawn to the rejection of claim 3 in Paper No. 20 are relevant to the instant rejection.

Applicant argues that a URL to the MEDAC website was previously submitted and submits an English language version of the website which gives information on the antibody, showing that the antibody is publicly available. The

argument has been considered but has not been found persuasive because an email request for information to the MEDAC website resulted in a reply from Maria Kleindel which specifically stated that "BM7 is not produced and therefore not available any more". See attached.

6. Claims 1, 3, 6-8, 20 and 24-26 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a "method for killing breast cancer cells or other carcinoma cells ..... in a cell population comprising nucleated peripheral blood cells" has no clear support in the specification and the claims as originally filed. A review of the specification reveals support for a cell population comprising nucleated cells in peripheral blood but no support for the newly added limitation. The subject matter claimed in claims 1, 3, 6-8, 20 and 24-26 broadens the scope of the invention as originally disclosed in the specification.

7. Claims 20, 21 and 25 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitations of a "relatively high toxicity" and "relatively low toxicity" recited in claim 20 and the limitation of low toxicity recited in claims 21 and 25 have no clear support in the specification and the claims as originally filed. The subject matter claimed in claims 20, 21 and 25 broadens the scope of the invention as originally disclosed in the specification.

8. Claims 3, 15, 16, 18, 19 are rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 20, Section 8, page 5 drawn to the rejection of claim 3.

Applicant's arguments drawn to the rejection of claim 3 in Paper No. 20 are relevant to the instant rejection.

Applicant argues that BM7 is publicly available. The argument has been considered but has not been found persuasive because contrary to Applicant's arguments, Maria Kleindel of MEDAC says that it is not publicly available.

9. Claims 1, 3, 6-8, 20, and 24-26 are rejected under 35 USC 112, second paragraph and the claims are indefinite because claim 1 recites the phrase "a recombinantly produced antibodies". The claims are confusing because it is not clear how one could produce "a recombinantly produced antibodies" which appear to be one antibody but also appear to be multiple antibodies.

10. Claims 1, 3, 6-8, 20 and 24-26 are rejected under 35 USC 112, second paragraph and the claims are indefinite because claim 1 recites the phrase "active toxin fragments". It is not clear what activity those active fragments have, for example are they antigens for the production of antibodies? Substrates for adducts? Toxic to cells?

11. Claim 20 is rejected under 35 USC 112, second paragraph and the claim is indefinite in the recitation of the terms "relatively high" and "relatively low". The terms are relative terms which renders the claim indefinite. The terms "relatively high" and "relatively low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

12. Claim 1, 13-14 and 24 are rejected under 35 USC 103 for the reasons previously set forth in Paper No. 20, Section 9, pages 5-7 drawn to the rejection of claims 1 and 14.

Applicant's arguments drawn to the rejection of claims 1 and 14 are relevant to the instant rejection.

Applicant argues that the claimed method provides surprising efficacy against malignant cells which would not be predicted by the references cited. None of the references cited either alone or in combination suggest that the combination would prove more effective than the sum of each alone. Applicant points to page 11, lines 14-17 to support the synergistic effects of the combined immunotoxins. Applicant further states that these results were unexpected and surprising. The argument has been considered but has not been found persuasive because only one example of synergy is presented wherein synergy is noted with antibodies selective for epitopes expressed on tumor but not normal cells. Since Applicant admits on the record that these results were unexpected and surprising, it could cannot be determined, nor would it be expected and or could it be predicted from the information in the specification or in the art of record that antibodies to epitopes other than those targeted would have the same effect.

13. All other objections and rejections recited in Paper No. 20 are withdrawn.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 21, 2002